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DIAGNOSING NUTRITIONAL DEFICIENCIES

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DIAGNOSING NUTRITIONAL DEFICIENCIES

Scientific advances in nutrition as well as the growing public interest in problems associated with food have stimulated an increased awareness of the prevalence and importance of malnutrition as a factor to be reckoned with in the interests of national welfare.

Extensive surveys of the diets of typical population groups throughout the United States have revealed that a large proportion of the populace subsists on diets which fall far short of desirable, or even minimum, nutritional standards. On the other hand, physicians and clinicians have, until very recently, been unable to report from their observations an incidence of malnutrition commensurate with that indicated by the results of diet surveys. The reason for this apparent discrepancy in findings becomes clear only when it is understood that, contrary to popular opinion, malnutrition is something which is by no means easily diagnosed or detected. Nutritionists and physicians are familiar with the classic clinical picture of pellagra, rickets, scurvy, beriberi and the like. With the exception of pellagra in the South, however, these full-blown conditions of malnutrition are met with comparatively rarely in this country. Further, in those instances where the general medical practitioner is unexpectedly confronted with one of these diseases in severe form, it may be some time before pathological causes are ruled out and the true nature of the disorder is recognized. Most important reason for the difficulty in diagnosing nutritional deficiencies is the fact that the nutritional state may vary by imperceptible degrees ranging from extreme and obvious malnutrition through progressively milder, outwardly undetectable stages, to comparative perfection. The great majority of nutritional deficiencies falls in the middle zone or subclinical condition of malnutrition characterized by subtle tissue changes rather than by gross, externally visible alterations. Lacking the typical symptoms of severe malnutrition as a guide, it is no wonder that diagnosticians often find it difficult to detect evidence of malnutrition.

The concept of nutritional deficiency as a matter of degree has led to a fuller understanding of the nature and existence of the subclinical manifestations of malnutrition. This in turn has stimulated the development of special clinical methods designed to detect these early, subacute stages of nutritional deficiency. Already the findings of these newer diagnostic methods have revealed a greater incidence of malnutrition than has been apparent to clinicians in the past. The results of diet surveys are now receiving corroboration and the wide prevalence of malnutrition is becoming recognized as a serious and significant public health problem.

General Diagnostic Methods:

Early Methods: At the beginning of the twentieth century nutritional status was diagnosed by physicians on the basis of physical or constitutional structure. Factors considered indicative of the state of nutrition included height and weight, deposits of subcutaneous fat, muscular development, posture, appearance of skin and mucous membranes and general vitality. These criteria were at best indirect and largely subjective means of evaluating nutritional status. In addition the results were subject to considerable error in interpretation because of wide variations in individual body build. More than a decade was spent in trying to improve the value of these measurements by establishing various height-weight formulas and indexes, but these attempts met with little success. Modification of the absolute weight criterion by studying weight-growth curves over a period of time offered a more satisfactory method of detecting severe malnutrition. This method too, however, has its limitations, especially in the crucial borderline zone where malnutrition is not outwardly manifested.

Deficiency Diseases: With the discovery of the vitamins and their specific effects on health, the concept of the dietary deficiency disease was formulated. This concept was soon extended to include disorders arising from deficiency of dietary essentials other than vitamins, namely proteins and the various minerals. The new knowledge of dietary essentials and the specific disorders induced by their deficiency made possible a new approach to the evaluation of nutritional status. This was the undertaking of surveys in which diets of various population groups were analyzed for deficiencies in the essential nutrients (1) .* Underlying this procedure is the assumption that evidence of substantial dietary deficiency indicates impaired nutritional status, usually in the form of deficiency diseases.

In addition to the dietary survey method, the new concept of deficiency diseases led to a more detailed clinical study of these diseases. It took some time for the symptoms of specific diseases to be recognized and differentiated since many of these diseases occur in multiple form. Over a period of years, the acute forms of these diseases have become defined by their individual characteristic symptoms. On the basis of such characteristic symptoms as the dermatitis of pellagra, the bleeding gums of scurvy or the bloodshot cornea of ariboflavinosis, the diagnosis of these acute forms of malnutrition is easily accomplished. Only recently, however, has it become recog-

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* See also *Borden's Review of Nutrition Research,* May, 1944, "Prevalence of Malnutrition as Indicated by Dietary Surveys."

nized that an individual may be suffering from a deficiency long before the obvious symptoms of the acute stage become evident. In this country particularly, the great majority of deficiency diseases occur in this chronic or subacute stage. For this reason they have gone unrecognized and untreated, despite the repeated indications of dietary surveys that malnutrition is of widespread occurrence.

Preliminary Diagnosis: The increasing awareness that deficiency diseases may be present without visible symptoms has led to the development of special clinical methods whereby the latent disorders may be detected. Before subjecting the patient to the complex routine of such diagnostic laboratory tests, however, some general, preliminary indications of malnutrition should be recognized. A practical, standard procedure for the early diagnosis of general malnutrition has been outlined by Spies (3) at the Nutrition Clinic in Birmingham, Alabama. The first step in this procedure is the careful study of the diet history. Although frequently far from accurate, the reported diet upon analysis may yield valuable clues as to the possible existence of a deficiency disease. Interpretation of the diet history is then followed by a complete medical history and physical examination. Spies describes the following criteria as suggestive of deficiency states:

> "When we have satisfied ourselves that the infants and children under our observation receive considerably less than the recommended allowances of essential nutrients, we are willing to accept the following symptoms as suggestive though not diagnostic of deficiency states: loss of desire for food and failure to gain weight; poor muscle tone, and aversion to play; abnormal tardiness in sitting, standing and walking, and pain on sitting or standing; insomnia; poor record in school; repeated respiratory infections; chronic diarrhea; photophobia, lacrimation, abnormal dryness and burning of the eyes; pallor; rough skin; fissures and maceration at the angles of the mouth; abnormally red tongue; increased pulse rate; beading of the ribs; enlarged wrists; square head, serious dental abnormalities, and Vincent's infection.
>
> "Likewise, in adolescents and adults, the following symptoms occurring in persons known to have ingested inadequate amounts of required nutrients suggest deficiency states: weakness, lassitude; loss of desire for food; loss of weight; failure of mental application; sore mouth or tongue; constipation or diarrhea; nervousness and irritability; paresthesia; night blindness; photophobia; burning and itching of the eyes; lacrimation; general pains in the muscles or joints; Vincent's infection; cheilosis; red, swollen lingual papillae; glossitis; stomatitis; vaginitis; poor muscle tone, loss of vibratory sensation; alteration of tendon reflexes; hypcresthesia of the skin; bleeding gums; dermatitis; abnormal pigmentation of the skin, particularly over points of pressure; rachitic chest deformity; anemia; abnormal dryness or conjunctival injection of eyes; vascularization of the cornea; inability of the eyes to accommodate properly."

Clinical Tests:

Following preliminary diagnosis on the basis of diet analysis, medical history and physical examination, positive diagnosis of deficiency disease and recognition of its exact nature can often be made through the use of special clinical tests recently developed (Table I.).

TABLE I. *Special Examinations for Detection of Malnutrition* (4)

Examination	Condition It May Detect
Roentgenogram of hand and wrist, elbow and hip	Rickets and scurvy in children; osteomalacia and scurvy in adults
Roentgenogram of heart.....	Advanced beriberi
Electrocardiogram	Changes suggestive of thiamine deficiency
Biomicroscopic eye examination with slit lamp	Capillary invasion of cornea (riboflavin deficiency); changes in conjunctivas (vitamin A deficiency)
Red blood cell count.....	Iron deficiency anemia; addisonian anemia; macrocytic anemia
Hemoglobin	
Stained blood smear	
Red blood cell volume	
Plasma ascorbic acid	Vitamin C undersaturation
Serum calcium	Vitamin D deficiency
Serum phosphatase	
Serum phosphorus	
Blood pyruvic acid	Vitamin B_1 deficiency
Serum protein or albumin	Protein deficiency
Blood prothrombin	Vitamin K deficiency

Based on the principle that the very early stages of malnutrition are reflected in the condition of the tissues, these tests are designed for the detection of such characteristic tissue changes as:

1. Lowered concentration of the essential factor in the blood
2. Depleted tissue stores
3. Diminished execretion of the essential factor
4. Microscopic changes in the depleted tissues
5. Gross structural and functional changes in tissues and organs

The tests commonly used to measure these changes may be classified into several basic groups – biochemical, microbiologic, biophysical (most of which are functional), and special clinical and morphologic, including biomicroscopic (5).

Biochemical and Microbiological: Most of the biochemical methods are designed for analysis of the blood and urine. These methods can be used for most of the vitamins, as well as for calcium, phosphorus, iron (as hemoglobin), and other minerals, and for plasma proteins.

In general, the biochemical methods are based on the reaction of a vitamin to yield a colored or fluorescent substance which may be measured quantitatively by colorimetric, fluorometric or titration procedures. Other tests involve the reaction of the vitamin with specific dyes; determination of vitamin-containing coenzymes in the blood; reaction of the vitamins with standard chemical reagents.

Several procedures are in use for collecting blood and urine samples to be tested by these methods. The blood level of the vitamin is determined on specimens collected before breakfast. For vitamins which are excreted in the urine, specimens collected for measurement may be obtained a few hours after the last meal or as a 24-hour sample. In this type of test, low values for the vitamin generally reflect a recent dietary deficiency, rather than a chronic condition. Still another procedure involves the response, after one, four or twenty-four hours, to a single test dose of the vitamin as determined by its absorption into the blood or its excretion in the urine. Low values in this type of test usually indicate not only recent dietary deficiency, but chronic tissue depletion. The results obtained by these methods must be carefully appraised before any meaningful conclusions may be drawn, allowance being made for the influence of such factors as transport, storage, utilization and excretion of the vitamin.

Microbiologic methods depend on the failure of a particular micro-organism to grow in the absence of a specific vitamin. The concentration of the vitamin in a test sample is measured by the extent to which it stimulates growth. The growth response of the micro-organism, in turn, is measured quantitatively by estimating the degree of turbidity produced in the culture.

(Applications): For purposes of illustration, the following examples of clinical tests employing biochemical methods are cited:

Vitamin A – Blood plasma sample is treated with a chloroform solution of antimony trichloride to yield a characteristic blue color in the presence of vitamin A (6). The color reaction may be measured quantitatively to indicate the exact concentration of the vitamin (7, 8, 9). In this test, carotene must also be determined and correction made for the blue color due to its presence.

Thiamin – The presence of thiamin may be detected by a reaction which causes the vitamin to be oxidized to thiochrome, a fluorescent pigment. The intensity of fluorescence is directly proportional to the concentration of thiamin (10).

Niacin – The amount of niacin in the blood may be determined by several methods which make use of the reaction between the vitamin, an aromatic amine and cyanogen bromide (11, 12).

Ascorbic Acid – Vitamin C is determined by its ability to reduce 2:6 dichloroindophenol and thereby produce a measurable color change (13).

Special methods have also been devised for estimating blood plasma levels of calcium, phosphorus, proteins, hemoglobin and the like. Suitable modifications of these same methods are used for estimating the amounts of these factors in the urine.

Biophysical: Biophysical methods have been designed to measure by special instruments functional or structural impairments caused by vitamin deficiencies. The measurement of dark adaptation as a criterion of vitamin A nutrition is a typical example.* Another application of biophysical methods is the measurement of capillary fragility under controlled pressure as an index of the vitamin C status of the body (14).

Disturbances in vitamin D or calcium metabolism were formerly tested biophysically by neuromuscular response to galvanic stimulus–a test for tetany (15), but this has been replaced by more modern biochemical methods for determining calcium levels in the blood.

Morphologic: Morphologic methods include the use of x-rays, the microscope and the biomicroscope. The x-ray has been used to detect rickets as well as very early stages of infantile scurvy by revealing defects in the deposition of bone calcium (16). More recently, the introduction of the biomicroscope for the examination of living tissue in the body has greatly furthered the detection of early deficiency states. Using this means of examination, Kruse has reported the occurrence of specific, biomicroscopically recognizable changes in at least four deficiency diseases. These microscopic changes have been observed in the tissues of the conjunctiva in vitamin A deficiency (17), in the cornea in ariboflavinosis (18, 19), in the tongue in niacin deficiency (20) and in the gum in deficiencies of vitamin C (21). By this means of examination it has been possible to detect the very earliest stages of these deficiency diseases, an achievement heretofore impossible by ordinary clinical methods.

As a result of biomicroscopic studies of the four specific deficiency diseases mentioned, Kruse (2) noted a similar pattern of biologic behavior common to each, despite the individuality of the symptoms manifested and the specificity of tissue affected. This led to the development of a new concept of the deficiency diseases in which definite stages (ranging from mild and severe chronic to mild and severe acute or combinations thereof) could be recognized in the development of all deficiency diseases. This concept was further elaborated to indicate the effect of the time element on the course and velocity of progress of the diseases, as well as on the speed of response of the various stages to therapeutic treatment. This has afforded new insight into the essential nature of these diseases and explains why the great majority of malnutrition cases heretofore have gone undetected.

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* See *Borden's Review of Nutrition Research*, December, 1943, "Nutrition and Vision—Vitamin A."

Evaluation of Methods:

The evaluation of existing methods for the detection of early nutritional deficiencies depends on a number of important criteria. These include, for purposes of mass surveys, simplicity, speed and reliability of the test and interpretation of the findings. A minimum of equipment and applicability to all age groups are further considerations. The method should also be capable of detecting the various forms, stages and degrees of the existing deficiency.

With these points in mind, it is possible to some extent to appraise the various types of methods mentioned in this Review. Biochemical and microbiologic methods on blood and urine have many advantages. These methods permit quick reflection of dietary habits, are useful in specific metabolic studies, and serve as an effective secondary screening process for persons without avitaminotic tissue changes. Their faults lie in the fact that they are often laborious and time-consuming. Further, tests of this type more frequently reflect immediate dietary influences. Such influences are first mirrored in the blood stream and only when they have existed for some time is there a change in the tissues. Thus, an isolated instance of a recent deficient diet would erroneously appear as a deficiency disease when judged by blood studies, while the existence of a chronic form of the deficiency might go undetected if the diet immediately preceding the blood test were a good one.

The biophysical methods, such as measurement of dark adaptation of the eye for vitamin A and capillary strength for vitamin C, have been very helpful and are usually fairly simple. It has been reported, however, that these methods have often failed to detect early stages of vitamin deficiency and that the symptoms which they do reveal may actually be manifestations of a much later stage.

The biochemical and biophysical methods, despite their limitations, however, do have their individual specific uses and are invaluable as sources of information on different aspects and stages of nutritional disturbances. As they are perfected, it is to be expected that their usefulness will be further enhanced.

Of the methods as they exist today, it is believed that those comprising gross and biomicroscopic examination of specific tissues for characteristic morphologic changes most nearly meet all of the previously listed requirements for satisfactorily appraising nutritional status. The biomicroscope can be used for all age groups, it is fairly simple to operate and can be used to detect all stages of a deficiency.

Prevalence of Malnutrition:

What have these newer diagnostic methods revealed with respect to the prevalence of malnutrition? According to Kruse (5) the largest part of malnutrition exists in the chronic state. Until recently, most of these chronic symptoms, regardless of degree, have not been recognized as specific characteristics of deficiency diseases. The use of gross and biomicroscopic methods for tissue examination has already revealed, however, that deficiency states of this type are highly prevalent. This correlates well with the results of dietary surveys. These results are not altogether surprising. As Kruse points out:

> "Even in high economic groups there are few people in absolutely perfect nutrition. Very few persons have consistently followed throughout life a diet satisfactory in all essentials, escaped the many other causes contributing to a deficiency state or had complete recovery from any impairment of their nutrition. The older the person, the more opportunity he has had for some dietary lapse or adverse influence. Then too the standard of perfection in the tissue is very exacting. And the biomicroscopic method is so sensitive that it is capable of detecting slight abnormalities. From all these considerations, the high prevalence of deficiency diseases is not unexpected."

Significance of Chronic Malnutrition:

Diet surveys and clinical tests indicate that there is a great deal of malnutrition in this country, most of which is present in chronic forms. The question naturally arises as to the importance of discovering and treating these marginal forms of malnutrition. How does a condition of sub-acute malnutrition affect the individual? If there are no outward signs of deficiency disease, as for example the characteristic lesions of scurvy or pellagra, is the individual functioning at lowered efficiency or experiencing any undesirable or ill effects? The evidence points increasingly to the fact that borderline malnutrition is a problem to be considered seriously and that detrimental effects, both immediate and long-range, do result. Most apparent of the immediate effects are sub-optimal health, mental depression, and a vague feeling of listlessness and irritability combined with various minor disturbances. Specifically, there may be symptoms of sensitivity to light or excessive watering of the eyes in mild riboflavin deficiency; psychic manifestations and perhaps gastrointestinal disturbances in mild thiamin deficiency, and similarly other symptoms peculiar to the mild stages of other deficiency states. As Kruse (5) points out, if diagnosis and treatment of mild and chronic deficiency states results in relief from these annoying minor symptoms, this can well be regarded as at least one important justification for the trouble and expense involved in detecting these conditions.

The importance of adequate tissue stores of the various nutritional essentials has also been pointed out in the well-known animal experiments of Sherman (22, 23) in which it has been shown that increasing the nutritional level above ordinary requirements, especially with respect to riboflavin, results in increased health and vigor, a longer "prime of life" and sturdier offspring. Nutrition studies with animals and human beings show, further, that in females particularly, adequate tissue stores of the nutritional essentials are of utmost importance with respect to the health and normalcy of the young.*

The further possibility that malnutrition may be implicated in the etiology of other diseases is another important consideration. The situation has been ably summed up by Kruse (5):

> "There are many strong intimations, short of proof, that malnutrition has a contributory or determining role in the occurrence of other diseases. This is the much debated question of the influence of nutritional status on morbidity. Up to now the lack of methods has made it difficult to supplant debate by demonstration on whether, or to what extent, impaired nutrition may play a part as a predisposing factor in parasitic diseases, such as tuberculosis, and whether satisfactory nutrition may aid in building up natural resistance against such diseases. With the present availability of methods, this very promising and hopeful vista may be explored. However, we must not look for too much from nutrition; we must not expect it to confer absolute protection against disease. Other circumstances, of course, exert their influence. Rather, let us say that nutrition at most may be one factor affecting the probability of disease occurring. If that should be demonstrated it would be sufficiently important to warrant evaluation of nutritional status as a routine procedure."

Conclusion:

The development of new clinical tests for the recognition of nutritional deficiencies has brought to light the fact that a great majority of these deficiencies exist in chronic or subclinical forms which are not readily apparent on the surface, but which have effects on health and well-being comparable to the more obvious and easily recognizable acute stages of malnutrition. The use of these clinical tests has not only facilitated the detection of borderline malnutrition but has greatly increased present understanding of the nature and significance of nutritional deficiency. These new diagnostic methods may well be regarded as another effective weapon in the eventual control and elimination of malnutrition.

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* See *Borden's Review of Nutrition Research* for November and December, 1944, "Dietary Causes of Congenital Abnormalities," and "Clinical Studies on Prenatal Nutrition."

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* Because of the exhaustive list of references pertaining to the various tests in this Review it is impossible in the space allotted, to give a complete bibliography. Representative authors, therefore, have been cited at random and do not necessarily represent the sole or pioneer workers in the field.

NEWS DIGEST

NOVEMBER CIDER – The natural taste of fresh November cider may now be available throughout the year in a new apple juice developed by the U. S. Department of Agriculture. The new product is a full-flavored apple juice concentrate which can be reconstituted, by the addition of water, to an apple juice which tastes and smells just like fresh apple cider. The concentrate is made by heating fresh apple juice rapidly enough to avoid changing its natural flavor, vaporizing the volatile flavoring constituents and then collecting them as a distilled essence. The juice from which the flavoring essence has been extracted is next concentrated by evaporation and the flavoring essence then added to the concentrate resulting in the production of a full-flavored self-preserving cider concentrate. *Science 100,* Suppl. 10 (Nov. 24) 1944.

CALCIUM DEFICIENCY—A low calcium diet has been found to induce the formation of ulcerative gastric lesions in experimental animals. These lesions resulted after the animals were maintained on a calcium deficient diet for only four weeks. Restoration to normal dietary levels prevents the lesions. Extension of the deprivation period to eight weeks resulted in larger ulcers and also markedly increased the tendency to bleeding. Whether calcium deficiency of comparable degree and duration may have a similar influence in the etiology of human gastric ulcer is a question which only further research may resolve. *Proc. Soc. Exp. Biol. Med. 57,* 1 (1944).

BIOTIN-PANTOTHENIC ACID – Biotin deficiency induced in experimental animals by the incorporation of certain sulfa drugs in a special purified diet has been found to be severely aggravated by a co-existing dietary deficiency in pantothenic acid. Animals deficient in biotin alone showed only mild symptoms such as the characteristic "spectacled eyes" and sparse fur. Animals deficient in pantothenic acid as well developed signs of biotin deficiency earlier than usual, suffered marked depression of growth and exhibited signs of a more severe biotin deficiency such as sore mouth, partial baldness and encrustations. The feeding of biotin protected the animals against these changes and also appeared to lessen the severity of the symptoms associated with pantothenic acid deficiency. The prophylactic administration of calcium pantothenate to biotin deficient animals not only protected against symptoms characteristic of pantothenic acid deficiency but also decreased the severity and retarded the development of the biotin deficiency manifestations. These experiments, therefore, indicate an important new interrelationship between the two vitamins, biotin and pantothenic acid. *Proc. Soc. Exp. Biol. Med. 57,* 47 (1944).

ABNORMALITIES DUE TO DIET—Latest findings on the effect of maternal dietary deficiency on the occurrence of congenital abnormalities in the offspring* confirm the importance of vitamin A with respect to normal eye development. Early nutrition experiments indicated that maternal nutritional deficiency was a possible factor in causing congenital blindness in animals; later experiments showed that in pigs, maternal deficiency of vitamin A, led to the birth of young without eyeballs or

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* See *Borden's Review of Nutrition Research* for November, 1944, "Dietary Causes of Congenital Abnormalities."

with partially developed eyes. Not until recently has this relationship been shown to apply to the usual laboratory animal—the rat—as well. Rats born of mothers raised on diets containing minute amounts of carotene (precursor of vitamin A) and bred on diets completely devoid of both carotene and vitamin A, exhibited various defects in the development of the eye. Only three out of twelve mothers succeeded in carrying their litters to or near term. The young, obtained by caesarian section, were all dead and all presented marked abnormal formation of the eyes. Sixty-two control females of the same strain on the same diet plus a supplement of vitamin A gave birth to over four hundred live young, all with normal eyes. *Proc. Soc. Exp. Biol. Med. 57,* 49 (1944).

NUTRITION IN BURNS—Proper nutritional care forms a vital part of the treatment of extensive burns. A recent report describes treatment of three cases of third degree burns covering respectively, 10, 30 and 50 per cent of the body. The patients were given high caloric and high nitrogen feedings in the form of dextrimaltose and amino acids. The nitrogen balance was followed throughout convalescence and the plasma proteins and body weight were determined periodically. All three patients were maintained in an excellent nutritional state. There seemed to be a mathematical relationship between the extent of surface burned and the amount of nitrogen required to maintain nutrition. Transfusions were reduced to a minimum. Amino acid preparations seem to be better tolerated and utilized than natural protein food and appear to be the solution to the problem of nutritional care of severe cases of protein drain. The development of shock following immediately on the first skin grafting is a phenomenon which may have an important bearing on the safety of this procedure in extensive burns. It is believed that in patients undergoing severe protein loss with protein synthesis barely keeping up with the loss, the opening up of new areas of the skin surface, with resulting increase in exudation and bleeding, would readily lead to the development of shock.—*Ann. Surg. 119,* 815 (1944).

VITAMIN C AND HEAT—Claims have been made that large ascorbic acid intakes are of immediate benefit in exposures to high temperature of relatively short duration. Three series of studies were conducted on 44 normal young men under rigidly controlled conditions of diet, physical work and environment. The ascorbic acid intake was set at two levels: 20 to 40 mg. and 520 to 540 mg. Particular attention was paid to (a) cardiovascular functions, (b) performance of standard physical tasks, (c) psychomotor functions and (d) ascorbic acid in sweat, blood plasma and urine. The performance of muscular work was studied in dry heat up to 122° F. The stay in the heat varied from three hours to four days. Comparisons were made between performances on a diet restricted in ascorbic acid intake and a diet supplemented by 500 mg. of ascorbic acid daily. The dietary differences were maintained for periods of four to seven days. Pulse rates in rest and in work, rectal temperatures, vasomotor stability tests, rates of sweating, general observations and subjective reports all failed to demonstrate significant advantage for the men receiving supplements of ascorbic acid. Psychomotor tests and strength tests likewise failed to show any advantage in the ascorbic acid supplementation. The total loss of vitamin C in the sweat was negligible. Heat exhaustion occurred with equal frequency in the vitamin C restricted and supplemented groups.—*Abstr. in J. Am. Med. Assoc. 126,* 591 (1944).